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10/061,961	02/01/2002	Douglas R. Smith	3431.1005-001	8757

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EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 04/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/061,961	SMITH ET AL.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *2-4,17,19 and 26-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-16,18 and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/4/2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/2003* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of Group I, claims 1, 2, 5-28, and 32, species of a second nucleotide associated with a fluorescently labeled nucleotide (claims 1, 5-16, and 18-25), species wherein multiple nucleotide variants at the position of said first nucleotide are tested simultaneously in the same reaction vessel by using more than one labeled primer (claim 18) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore, claims 1, 5-16, 18, and 20-25 will be examined.

Specification

2. The disclosure is objected to because of the following informalities: note that primers ASM39-3'T and A47-3'T in last paragraph of page 31 and primers ASM29-3' T and ASM47-3' T in last paragraph of page 33 have more 10 nucleotides. However, these primers have no SEQ ID Nos. Furthermore, these primers have not included in the sequencing listing. Please clarify. See 37 CFR 1.821 through 1.825.

Appropriate correction is required.

Claim Objections

3. Claim 1 is objected to because of the following informalities: (1) "in the event" in lines 8, 14, and 16 should be "in the event that "; (2) "in the event of " in line 10 should be "in the event that "; and (3) add "to said first nucleotide" in the end of "forming" step.

4. Claims 5 and 11 are objected to because of the following informality: add "to said first nucleotide" in the end of "forming" step.

5. Claims 9 and 15 are objected to because of the following informalities: (1) "Ångstroms" should be "angstroms"; and (2) "a Förster radius of greater than 30 Angstroms" should be "a Förster radius greater than 30 Angstroms".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 5-16, 18, and 20-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 is rejected as vague and indefinite because it is unclear what means "opposite said first nucleotide position". Does this phrase means a position at said primer that is hybridized to said first nucleotide position in a complex formed by said strand of DNA and said primer. Please clarify.

9. Claim 1 recites the limitation "said fluorescently labeled nucleotide product" in the claim. There is insufficient antecedent basis for this limitation in the claim because the claim does not describe that a detectable label associated with a second nucleotide is a fluorescent label. Please clarify.

10. Claim 1 recites the limitation "said fluorescently labeled nucleotide excision product" in the claim. There is insufficient antecedent basis for this limitation in the claim because there is no phrase "a fluorescently labeled nucleotide excision product" in the claim. The examiner suggests changing "a fluorescently labeled nucleotide product" in line 14 into "a fluorescently labeled nucleotide excision product". Please clarify.

11. Claim 1 is rejected as vague and indefinite because "fluorescent label associated with an excess of said nucleotide excision product is indicative of the absence of said first nucleotide" is not 100% correct statement. As shown in the claim, said second nucleotide is preferentially excised to form a fluorescently labeled nucleotide product in the event that said second nucleotide is not hybridized to said first nucleotide. Therefore, detection of said excision product is indicative of the absence of said first nucleotide or indicates that said second nucleotide is not hybridized to said first nucleotide. Furthermore, since said excision product is labeled with a fluorescent label, it is unclear that fluorescent label in the phrase "fluorescent label associated with an excess of said nucleotide excision product is indicative of the absence of said first nucleotide" is different from the fluorescent label of said nucleotide excision product or not. Since detection of said excision product is indicative of the absence of said first nucleotide or indicates that said second nucleotide is not hybridized to said first nucleotide, it is unclear why only an excess of said excision product is indicative of the absence of said first nucleotide and an amount of said excision product is not indicative of the absence of said first nucleotide. Please clarify.

12. Claim 1 is rejected as vague and indefinite in view of "fluorescent label associated with an excess of said extension product is indicative of the presence of said first nucleotide". Since

detection of said extension product is indicative of the presence of said first nucleotide, it is unclear why only an excess of said extension product is indicative of the presence of said first nucleotide and an amount of said extension product is not indicative of the presence of said first nucleotide. Please clarify.

13. Claims 5, 6, 11, and 12 are rejected as vague and indefinite because it is unclear what means "opposite the position of the first nucleotide". Does this phrase means a position at said primer that is hybridized to said first nucleotide position in a complex formed by said strand of DNA and said primer. Please clarify.

14. Claims 5 and 11 recite the limitation "the fluorophore" in the claim. Since the quencher recited in the claims can be a fluorophore, it is unclear that "the fluorophore" means the fluorescent label or the quencher. Please clarify.

15. Claims 5 and 11 are rejected as vague and indefinite. Since only primer has a fluorophore and the sample recited in the claim does not have a fluorophore, it is unclear how to monitoring the sample for emission from the fluorophore. Please clarify.

16. Claims 5 and 11 are rejected as vague and indefinite because it is unclear what means that "the presence of fluorescence emission at levels greater than background being indicative of the absence of the first nucleotide". Does this phrase mean that the presence of fluorescence intensity at the emission wavelength of the fluorophore at levels greater than background being indicative of the absence of the first nucleotide. Since the quencher can be a fluorophore, it is unclear that "the fluorophore" is the quencher or not. Please clarify.

17. Claims 5 and 11 are rejected as vague and indefinite because it is unclear what means that "the absence of fluorescence emission being indicative of the presence of the first nucleotide" since each fluorophore has an excitation wavelength and an emission wavelength. Please clarify.

18. Claims 9 and 15 is rejected as vague and indefinite in view of the phrase "said quencher display a Förster radius of greater than 30 Angstroms". Since it is known that Förster radius means a distance between two fluors where the efficiency of energy transfer is equal to 50% (for example, see US Publication 20030211454), said quencher itself can not display a Förster radius. Furthermore, it is known that Förster radius between a donor and a quencher must be in certain range in order to perform fluorescent energy transfer. However, there is no up limit for Förster radius in the claim. Please clarify.

19. Claim 18 recites the limitation "multiple nucleotide variants" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no "multiple nucleotide variants" in claims 1, 5, and 11. Please clarify.

20. Claim 18 recites the limitation "the same reaction vessel" in the claim. There is insufficient antecedent basis for this limitation in the claim since there is no "reaction vessel" in claims 1, 5, and 11. Furthermore, there is no more than one labeled primer in claims 1, 5, and 11. Please clarify.

21. Regarding claim 22, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

23. Claims 5, 8, 10, 11, 14, 16, 20-23, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Nezarenko *et al.*, (US Patent No. 5,866,336, published on February 2, 1999).

Nezarenko *et al.*, teach nucleic acid amplification oligonucleotides with molecular energy transfer labels and methods based thereon.

Regarding claim 5, since 5' nucleotide of the hairpin primer taught by Nezarenko *et al.*, is either a fluorescent label or a quencher (see column 42, third paragraph), step A of Figure 3 teaches forming an admixture of a primer (ie., primer R) and a strand of DNA in said sample and imposing conditions such that a hybridization product is formed between the primer and said DNA strand, said primer comprising a sequence of DNA which hybridizes with the strand of DNA and having a second nucleotide containing a fluorescent label and said primer also containing a quencher attached at a position adjacent to said second nucleotide, the second nucleotide hybridizing to the first nucleotide in the event that the second nucleotide is complementary to the first nucleotide and the second nucleotide not hybridizing to the first nucleotide in the event that the second nucleotide is not complementary recited in "forming " step of claim 5 (see attached Figure 3 with the examiner's handwritings and column 9, lines 15-20). Since the DNA polymerase used in Figure 3 has 5'-3' exonuclease activity (see column 9, lines 15-20), steps B to D of Figure 3 teach applying a proofreading polymerase to the

hybridization product under conditions in which the second nucleotide containing the fluorescent label is preferentially excised in the event that the second nucleotide is not hybridized to the first nucleotide as recited in "applying" step of claim 5 see attached Figure 3 with the examiner's handwritings and column 42, third paragraph). Since the quencher taught by Nezarenko *et al.*, is a fluorophore (see Figures 1A and 1B, and column 9, lines 3-6), Nezarenko *et al.*, teach that detection of fluorescence from the quencher in the amplified product indicates the absence of the first nucleotide in the said strand of DNA wherein the first nucleotide is capable of complementary to the second nucleotide as recited in claim 5.

Regarding claim 11, step A of Figure 3 teaches forming an admixture of a primer (ie., primer R) and a strand of DNA in said sample and imposing conditions such that a hybridization product is formed between the primer and said DNA strand, said primer comprising a sequence of DNA which hybridizes with the strand of DNA and having a second nucleotide containing a quencher and said primer also containing a fluorescent label attached at a position adjacent to said second nucleotide, the second nucleotide hybridizing to the first nucleotide in the event that the second nucleotide is complementary to the first nucleotide and the second nucleotide not hybridizing to the first nucleotide in the event that the second nucleotide is not complementary recited in "forming " step of claim 11 (see attached Figure 3 with the examiner's handwritings and column 9, lines 15-20). Since the DNA polymerase used in Figure 3 has 5'-3' exonuclease activity (see column 9, lines 15-20), steps B to D of Figure 3 teach applying a proofreading polymerase to the hybridization product under conditions in which the second nucleotide containing the quencher is preferentially excised in the event that the second nucleotide is not hybridized to the first nucleotide as recited in "applying" step of claim 11 (see attached Figure 3

with the examiner's handwritings). Since the amplified product in step D of Figure 3 has a fluorescent label (see attached Figure 3 with the examiner's handwritings), Nezarenko *et al.*, teach that detection of fluorescence in the amplified product indicates the absence of the first nucleotide in the said strand of DNA wherein the first nucleotide is capable of complementary to the second nucleotide as recited in claim 11.

Regarding claims 6 and 11, Nezarenko *et al.*, teach that said quencher moiety (ie., said energy acceptor moiety) is attached about 1-10 nucleotides away from the position of the fluorescent label (ie., said energy donor moiety) on said second nucleotide as recited in claims 6 and 11 (see claim 7 in column 58).

Regarding claims 8, 10, 14, and 16, since Nezarenko *et al.*, teach the hairpin primers are labeled with FAM/DABCYL (see column 59, claims 12 and 13), claims 8, 10, 14, and 16 are anticipated by Nezarenko *et al.*.

Regarding claims 20-22, since, the amplification reaction taught by Nezarenko *et al.*, is a PCR (see attached Figure 3 with the examiner's handwritings and column 9, lines 15-20) which includes a cycled hybridization and extension, Nezarenko *et al.*, disclose the amplification reactions recited in claims 20-22. Since, during the process of the PCR taught by Nezarenko *et al.*, more 5' nucleotides with a fluorescent label or a quencher are generated from the hairpin primer and more extension products are generated, the amount of said nucleotide excision product and of said extension product are increased by means of an amplification recited in claims 20-22.

Regarding claim 24, Nezarenko *et al.*, teach that said DNA of the sample is genomic DNA (see column 19, second paragraph).

Regarding claim 25, since Nezarenko *et al.,* teach that 5' nucleotide with a fluorescent label or a quencher is released from the hairpin primer by 5'-3' exonuclease activity of the polymerase (see column 42, third paragraph), Nezarenko *et al.,* disclose that said primer further comprises a tail (ie., 5' nucleotide) that is non-complementary with said DNA strand (see Figure 3 and column 42, third paragraph).

Therefore, Nezarenko *et al.,* teach all limitations recited in claims 5, 8, 10, 11, 14, 16, 20-23, and 25.

24. Claims 7 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Nezarenko *et al.,* (February 2, 1999) as applied to claims 5, 8, 10, 11, 14, 16, 20-23, and 25 above as evidence by Haugland (Handbook of Fluorescent probes and Research Chemicals, Sixth Edition, 1998, pages 19 and 20).

The teachings of Nezarenko *et al.,* have been summarized previously, *supra.* Since the fluorescent label on the hairpin primer taught by Nezarenko *et al.,* is FAM and it is known that the wavelength for absorption maximum of FAM such as C 1359 is 492 nm while the wavelength for emission maximum of FAM such as C 1359 is 518 nm (see Haugland, page 20, left column and 1.3 Data Table), Nezarenko *et al.,* as evidence by Haugland disclose that said fluorophore (ie., FAM) is a fluorescent label having an absorption maximum in a wavelength range between 340 nm and 820 nm and an emission maximum in a wavelength range between 370 nm and 850 nm as recited in claims 7 and 13.

Claim Rejections - 35 USC § 103

25. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

26. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nezarenko *et al.*, (February 2, 1999) as applied to claims 5, 8, 10, 11, 14, 16, 20-23, and 25 above, and further in view of Burke *et al.*, (US Patent No. 6,511,815 B1, filed on December 20, 1999).

The teachings of Nezarenko *et al.*, have been summarized previously, *supra.* Since claim 5 of this instant application includes all limitations recited in "forming" and "applying" steps of claim 1, Nezarenko *et al.*, teach "forming" and "applying" steps of claim 1.

Nezarenko *et al.*, do not disclose monitoring said sample for the presence of a fluorescent label using fluorescent polarization as recited in claim 1. However, Nezarenko *et al.*, teach monitoring said sample for the presence of a fluorescent label using fluorescence spectroscopy that is commonly used to monitor intensity of fluorescent signals (see column 38).

Burke *et al.*, teach method for quantitating competitive binding of molecules to proteins utilizing fluorescence polarization. An advantage of fluorescence polarization over fluorescence intensity is the ability to remove unrelated factors from the measurement, such as other molecules which adversely affect intensity (see column 6, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 in view of the patents of Nezarenko *et al.*, and Burke *et al.*. One having ordinary skill in the art would have been motivated to do so because an advantage of fluorescence polarization over fluorescence intensity is the ability to remove unrelated factors from the measurement, such as other molecules which adversely affect intensity (see Burke *et al.*, column 6, second paragraph) and the simple replacement of one well known fluorescence detection method (i.e., a method taught by Nezarenko *et al.*,) from another well known fluorescence detection method (i.e., fluorescence polarization taught by Burke *et al..*,) during the process of performing the method recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because fluorescence detection method taught by Nezarenko *et al.*, and fluorescence detection method taught by Burke *et al.*, are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

27. Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nezarenko *et al.*, (February 2, 1999) as applied to claims 5, 8, 10, 11, 14, 16, 20-23, and 25 above, and further in view of Tyagi *et al.*, (US Patent No. 6,277,607 B1, filed on May 24, 1999).

The teachings of Nezarenko *et al.*, have been summarized previously, *supra.* Since target nucleic acid template used by Nezarenko *et al.*, can be cDNA (see page 19, second paragraph), which is commonly cloned in a plasmid vector, target nucleic acid template used by Nezarenko *et al.*, can be circular DNA.

Nezarenko *et al.*, do not disclose that the amount of said nucleotide excision product and said extension product is amplified by means of rolling circle amplification (RCA) after circularization of said DNA strand in the sample as recited in claim 23.

Tyagi *et al.*, teach a nucleic acid amplification using either PCR or RCA.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 23 in view of the patents of Nezarenko *et al.*, and Tyagi *et al.*. One having ordinary skill in the art would have been motivated to do so because Tyagi *et al.*, have successfully used RCA to amplify a nucleic acid and the simple replacement of one well known amplification method (i.e., PCR taught by Nezarenko *et al.*,) from another well known amplification method (i.e., RCA taught by Tyagi *et al.*,) during the process of performing the method recited in claim 23 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because PCR method taught by Nezarenko *et al.*, and RCA taught by Tyagi *et al.*,, are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

28. Claims 1 20, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shultz *et al.*, (US Patent No. 6,391,551 B1, filed on August 25, 1999) in view of Burke *et al.*, (December 20, 1999).

Shultz *et al.*, teach detection of nucleic acid hybrids.

Regarding claim 1, Shultz *et al.*, teach a method for determining the presence or absence of a first endogenous nucleic acid target in a nucleic acid sample containing that target or a substantially identical second target that comprises the steps of: (A) admixing said sample having a first and second endogenous nucleic acid targets to be assayed with one or more nucleic acid probes to form a hybridization composition, wherein said first and second endogenous nucleic acid targets comprise a region of sequence identity except for at least a single nucleotide at a predetermined position that differs between the endogenous targets, and wherein said nucleic acid probe (i) is substantially complementary to said nucleic acid target region of sequence identity and comprises at least one nucleotide at an interrogation position, said interrogation position of the probe being aligned with said predetermined position of a target when a target and probe are hybridized and (ii) includes an identifier nucleotide in the 3'-terminal region; (B) maintaining said hybridization composition for a time period sufficient to form a treated sample wherein the nucleotide at said interrogation position of said probe is aligned with the nucleotide

at said predetermined position of said target in said region of identity; (C) admixing the treated sample with a depolymerizing amount an enzyme whose activity is to release one or more nucleotides from the 3'-terminus of a hybridized nucleic acid probe to form a treated reaction mixture; (D) maintaining the treated reaction mixture for a time period sufficient to release identifier nucleotide and depolymerize said hybridized nucleic acid probe; and (E) analyzing for the presence of released identifier nucleotide to obtain an analytical output, said analytical output indicating the presence or absence of said nucleotide at said predetermined region and thereby the presence or absence of a first or second nucleic acid target wherein said analytical output is obtained by fluorescence spectroscopy and said identifier nucleotide is fluorescently labeled after release from said hybrid (e.g., see claims 30-32 in columns 160 and 161). Since Shultz *et al.*, teach admixing said sample having a first and second endogenous nucleic acid targets to be assayed with one or more nucleic acid probes to form a hybridization composition, wherein said first and second endogenous nucleic acid targets comprise a region of sequence identity except for at least a single nucleotide at a predetermined position that differs between the endogenous targets, and wherein said nucleic acid probe (i) is substantially complementary to said nucleic acid target region of sequence identity and comprises at least one nucleotide at an interrogation position, said interrogation position of the probe being aligned with said predetermined position of a target when a target and probe are hybridized and (ii) includes an identifier nucleotide in the 3'-terminal region and maintaining said hybridization composition for a time period sufficient to form a treated sample wherein the nucleotide at said interrogation position of said probe is aligned with the nucleotide at said predetermined position of said target in said region of identity (see above), Shultz *et al.*, disclose forming an admixture of a primer (ie, one nucleic acid probe

taught by Shultz *et al.*,) and said strand of DNA in said sample and imposing hybridization conditions on said primer and said DNA strand to form a hybridization product, said primer comprising a sequence of DNA which hybridizes with said strand of DNA adjacent to said first nucleotide position (ie., a predetermined position taught by Shultz *et al.*,) and having a second nucleotide associated with a fluorescent label (ie., a fluorescent labeled identifier nucleotide taught by Shultz *et al.*,), said second nucleotide hybridizing to said first nucleotide in the event that said second nucleotide is complementary to said first nucleotide and said second nucleotide not hybridizing to said first nucleotide in the event that said second nucleotide is not complementary to said first nucleotide as recited in claim 1. Since Shultz *et al.*, teach admixing the treated sample with a depolymerizing amount an enzyme whose activity is to release one or more nucleotides from the 3'-terminus of a hybridized nucleic acid probe to form a treated reaction mixture (see above) wherein the enzyme with a depolymerizing activity is a polymerase (e.g., see column 23), Shultz *et al.*, disclose applying a proofreading polymerase to the hybridization product under conditions in which said second nucleotide is preferentially excised to form a fluorescently labeled nucleotide product in the event that said second nucleotide is not hybridized to said first nucleotide as recited in claim 1. Since Shultz *et al.*, teach analyzing for the presence of released identifier nucleotide to obtain an analytical output, said analytical output indicating the presence or absence of said nucleotide at said predetermined region wherein said analytical output is obtained by fluorescence spectroscopy (see above), Shultz *et al.*, disclose monitoring said sample for the presence of a fluorescent label in association with at least one of said fluorescently labeled nucleotide excision product wherein detection of said nucleotide excision product is indicative of the absence of said first nucleotide (a nucleotide at a

predetermined position taught by Shultz *et al.*,) that is complementary to said second nucleotide as recited in claim 1.

Regarding claim 20, Since, during the process of amplification taught by Shultz *et al.*, more 3' nucleotides with a fluorescent label are generated from the primer and more extension products are generated (e.g., see claims 30-32 in columns 160 and 161), the amount of said nucleotide excision product and of said extension product are increased by means of an amplification recited in claim 20. .

Regarding claim 24, since the sample used by Shultz *et al.*, comprises genomic DNA (see column 21), claim 24 is anticipated by Shultz *et al.*.

Regarding claim 25, since Shultz *et al.*, teach that 3' nucleotide with a fluorescent label is released from the primer by 3'-5' exonuclease activity of the polymerase (see columns 160-162, see claims 30-32 and 47), Shultz *et al.*, disclose that said primer further comprises a tail (ie., 3' nucleotide) that is non-complementary with said DNA strand as recited in claim 25.

Shultz *et al.*, do not disclose monitoring said sample for the presence of a fluorescent label using fluorescent polarization as recited in claim 1. However, Shultz *et al.*, monitoring said sample for the presence of a fluorescent label using fluorescence spectroscopy (see above) that is commonly used to monitor intensity of fluorescent signals.

Burke *et al.*, teach method for quantitating competitive binding of molecules to proteins utilizing fluorescence polarization. An advantage of fluorescence polarization over fluorescence intensity is the ability to remove unrelated factors from the measurement, such as other molecules which adversely affect intensity (see column 6, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 1 in view of the patents of Shultz *et al.*, and Burke *et al.*. One having ordinary skill in the art would have been motivated to do so because an advantage of fluorescence polarization over fluorescence intensity is the ability to remove unrelated factors from the measurement, such as other molecules which adversely affect intensity (see Burke *et al.*, column 6, second paragraph) and the simple replacement of one well known fluorescence detection method (i.e., a method taught by Shultz *et al.*,) from another well known fluorescence detection method (i.e., fluorescence polarization taught by Burke *et al..*,) during the process of performing the method recited in claim 1 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because fluorescence detection method taught by Shultz *et al.*, and fluorescence detection method taught by Burke *et al.*, are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Conclusion

29. No claim is allowed.

30. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is either (703)872-9306 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571)272-0782.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

Frank Lu
PSA
April 9, 2004

FRANK LU
PATENT EXAMINER

a part of the office action

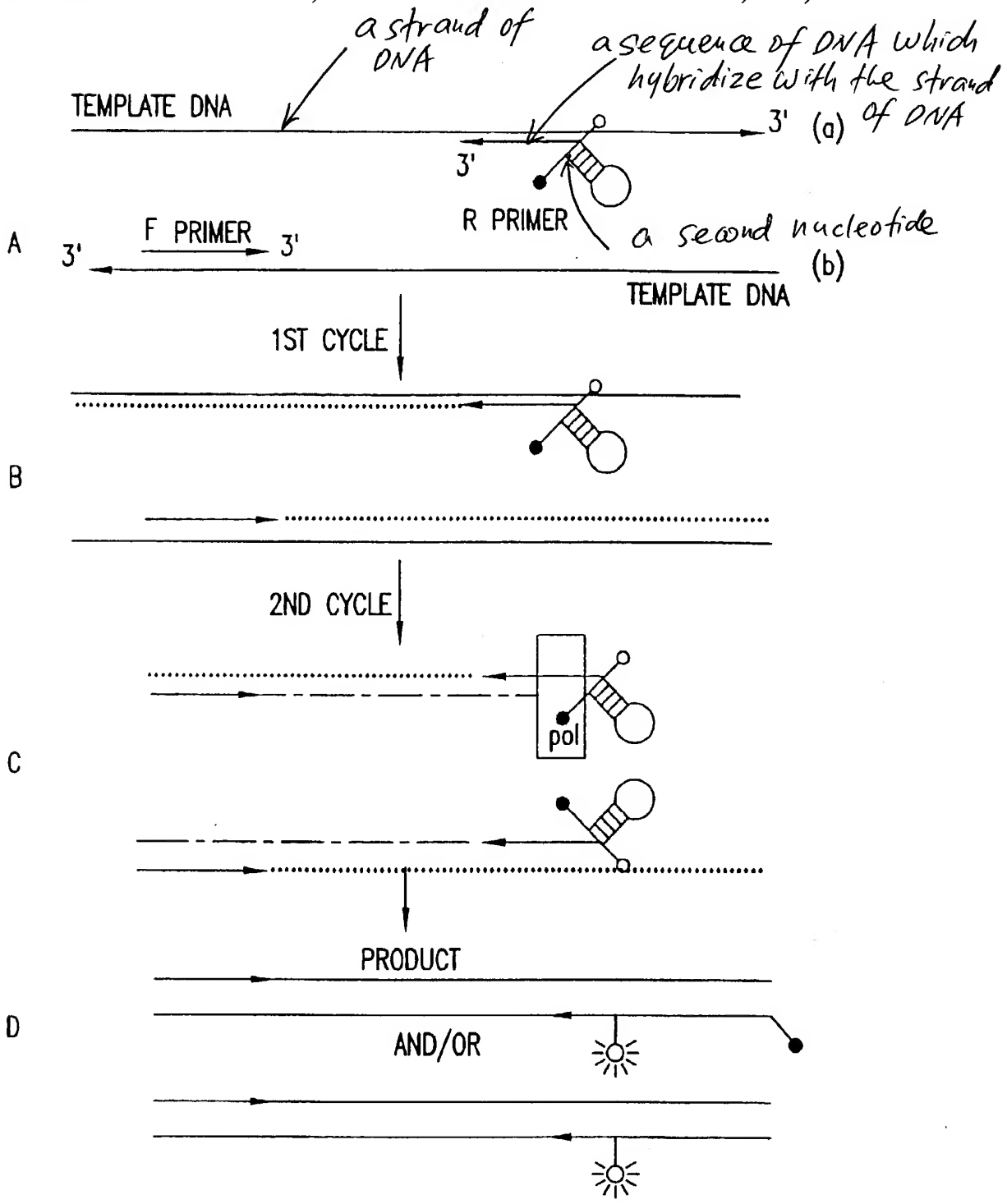

FIG.3